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COMPOSITIONS WITH ENHANCED PENETRATION

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(57) Claim

Transdermal delivery systems are not always efficacious due to such factors as the failure of the drug to sufficiently penetrate the cutaneous membrane and enter the body to produce therapeutic systemic effects. The present invention uses a novel penetration enhancer to deliver efficacious amounts of the desired drug to the body. The compositions and methods of the instant invention have several advantages over conventional systems for the delivery of drugs.

1. A transmembranally administerable composition comprising:
   (a) about 0.2% to about 5% of therapeutically active medicament of bioaffecting agent,
   (b) about 0% to about 99.8% of solvent, and
   (c) about 0% to about 15% of gelling agent.

2. A composition of Claim 1 wherein the therapeutically active medicament bioaffecting agent is selected from the group consisting of diphenhydramine, tetrahydroaminoacridine, atenolol, tazifylline, 2-Methoxy-4-[2-(5-methyl-1H-pyrazol-3-yl)ethenyl] phenol or a pharmaceutically acceptable salt thereof.

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4. A method of administering a bioaffecting agent comprising contacting a composition of Claim 1 with a living membrane.

ABSTRACT

The penetration of various drugs through living membranes is improved by their use in transdermal compositions containing certain penetration-enhancing systems.

BACKGROUND OF THE INVENTION

Diphenhydramine, hydrochloride (Benadryl®, or 2-(diphenylmethoxy) N, N-dimethylethylamine), is known to be useful for its antihistaminic, anticholinergic, antitussive, antiemetic, and sedative properties. The compound and its preparation are described in US Patent 2,241,714 which is hereby incorporated by reference.

The base is a liquid and its salts have acceptable solubilities in standard liquid media. Thus, diphenhydramine-based drugs are conventionally used in dosage forms such as oral and parenteral. However, there are undesirable digestive side effects possible with oral formulations. Generally there are compliance problems with parenterals.

Diphenhydramine is a nonprescription drug widely used alone or in combination with other drugs as an effective antihistamine with a sedative side effect. Carruthers, et al (Clin Pharmacol Ther 1978; 23:375-382) showed that the sedative side effect of diphenhydramine hydrochloride could be eliminated if the blood concentration remains in the range of 25 to 50 ng/ml (equivalent to 21.9 to 43.9 ng/ml diphenhydramine base). This indicates that a sustained dosage form which could provide such constant blood levels would be a very useful and viable dosage form in the treatment of allergy.

Tetrahydroaminoacridine, 1,2,3,4-tetrahydro-9-acridinamine Tacrine, THA), a very old compound is known to be useful as a respiratory stimulant and has anticholinesterase activity. It has been shown that THA improves the amnesia characteristic of Alzheimer's disease (Brinkman and Gershon, 1983; Flood et al, 1985; Rathman and Conner, 1984; McGeer, 1984).

Tazifylline is known to be useful as an antihistamine. It is covered in US Patent 4,374,835 which is hereby incorporated by reference.

Atenolol, 4-[2-hydroxy-3-[(1-methylethyl)amino]-propoxy]benzeneacetamide, is covered in US Patents 3,663,607 and 3,836,671 hereby incorporated by reference. It is a β-adrenergic blocker.

2-Methoxy-4-[2-(5-methyl-1H-pyrazol-3-yl)ethenyl]-phenol is covered in pending application 861,179. It has antiasthma, antiallergy, antiinflammatory, antipsoriatic, analgesic, and cardiovascular activities.

While the above drugs are highly efficacious, their use is subject to such problems as dose dumping and high drug use requirements.

United States Patent No. 4,611,008 discloses the use of Miglyol-812 or Miglyol-829 in a coronary-active gel-containing preparation.

United States Patent No. 4,331,651 covers in part, caprylic/capric acid -1,2-propanediol diester used as a release-promoting substance used in a silicone rubber carrier for an active ingredient.

United States Patent No. 4,336,243 covers a microsealed transdermal delivery pad for nitroglycerin administration which contains a silicon matrix having microsealed compartments of silicone rubber mixed with a hydrophilic solvent system, the solvent system can contain a saturated coconut oil such as miglyol oil which improves the transport and absorption of the nitroglycerin.

SUMMARY OF THE INVENTION

It has been discovered that therapeutically active agents such as diphenhydramine, tetrahydraminoacridine, atenolol, tazifylline, 2-methoxy-4-[2-(5-methyl-1H-pyrazol-3-yl)ethenyl]phenol, and the like in combination

with a solvent, Miglyol® oil and/or a gelling agent such as Aerosil® 200 a higher flux value than formulations without Miglyol® oil when applied on skin.

Gastrointestinal problems associated with some drugs which are administered orally are thus eliminated. The gradual release of a drug via a membranal tissue minimizes the risk of dose dumping and other side effects.

In addition, the use of the present invention would result in a reduction in overall drug load dose. Furthermore, a patch or other transmembranal device serves as a reminder to the patient to administer the proper dosage.

These and other advantages of the invention will become apparent upon consideration of the following description of the invention.

In a preferred embodiment of the instant invention, a transmembranal composition of diphenhydramine or a pharmaceutically acceptable salt thereof is combined with Miglyol®, a gelling agent and an alcohol in the form of a gel. The gel would be on a controlling or a noncontrolling membrane compatible with manufacturing processes and capable of providing the desired flux of the active ingredient. Microporous membranes, Silastic® membranes, and/or polyurethane (with polyester or polyether backbone) membranes among others may be used.

The side effects often associated with the use of diphenhydramine in oral and parenteral formulations can be overcome by administration of the drug via topical application to body membranes for absorption into the system.

Transdermal delivery systems are not always efficacious due to such factors as the failure of the drug to sufficiently penetrate the cutaneous membrane and enter the body to produce therapeutic systemic effects. The present invention uses a novel penetration

enhancer to deliver efficacious amounts of the desired drug to the body. The compositions and methods of the instant invention have several advantages over conventional systems for the delivery of drugs. One principal advantage concerns the undesirable side effects associated with administration via dosage forms which are swallowed or injected. For instance, the nausea and/or other gastrointestinal discomfort associated with liquids and solids which are swallowed is eliminated when transmembrane administration is employed. The compositions of the instant invention are introduced into the body via various membranes, for example, transdermally, buccally, rectally, and nasally.

Also, the storage and transportation problems associated with liquid dosage forms are generally eliminated when transmembrane administration is employed. These are usually creams, gels, and solid suppositories. In the compositions of the instant invention the topical delivery of the drugs has several advantages. One such is the gradual release of the drug via membranal tissue, for example, on the skin or in the nasal passages, minimizes the risk of dose dumping and can also reduce the overall drug loading dose. Also, a patch or other transdermal device serves as a reminder to the patient to administer the proper dosage of the drug.

These and other advantages of the invention will be apparent upon the following description of the invention.

DETAILED DESCRIPTION

The present invention concerns a composition for use in transmembranal administration of drugs. Such a composition comprises (a) about 0.1% to about 50% by weight of one or more drugs selected from the group

consisting of diphenhydramine, tetrahydroaminoacridine, atenolol, tazifylline, 2-Methoxy-4-[2-(5-methyl-1H-pyrazol-3-yl)ethenyl]phenol and the like and the pharmaceutically acceptable salts thereof, (b) about 0% to about 99.8% by weight of a solvent, (c) about 0% to about 15% by weight of a gelling agent and other excipients or diluents as would occur to one skilled in the art.

All percentages recited herein are weight percentages based on total composition weight unless otherwise specified.

The term diphenhydramine and pharmaceutically acceptable salts thereof is intended to include all forms of diphenhydramine and/or its analogs which have medical utility. Thus, diphenhydramine, its hydrochloride salt, and the like are contemplated. Mixtures may also be used.

While the use of a diphenhydramine-based drug is an example of a transmembranal formulation, the use of other beneficial substances is also contemplated. Thus sedatives, tranquilizers, antiinfectives, cardiotonics, cognition activators, and the like may be included in the compositions of the invention.

Generally the drug component will comprise about 0.1% to about 50%, preferably about 1 to about 30%, and most preferably about 2 to about 10% by weight of the total composition.

Other components such as alcohol and a gelling agent are also contemplated. A preferred gelling agent is Aerosil® 200. All acceptable excipients, antioxidants, preservatives, including Wickenol® 535 and Vit. E.

A controlling membrane is also contemplated. Preferred membranes include microprous membranes, Silastic® membrane, polyurethane membranes, and the like.

A method of administering the above composition includes (a) contacting the drug with a vehicle to produce a transmembranal formulation and (b) applying that formulation in a suitable device to body membrane for absorption therethrough.

Other conventional adjuncts, for example, colorants, perfumes, stabilizers, and the like can also be employed in compositions of the present invention.

While the use of a diphenhydramine-based drug are essential to the composition, the use of other beneficial substance is also contemplated and may be used in the composition.

The permeation-enhancing portion of the instant invention is a substance which functions to assist in the migration of the drug component(s) through the membranes and into the bloodstream. Thus, any agent(s) which function to hasten and/or to regulate the transmembranal passage or systemic release of drug(s) can be used in combination with Miglyol 840.

Generally the solvent, the permeation-enhancing component, will comprise about 0.1 to 99.9%, preferably to 80%, and most preferably 50 to 80% by weight of the total composition. The action ingredient permeates through the skin as a neat drug (base) or in formulations containing a solvent.

The solvent component will comprise at least one solvent for the drug component. Useful solvents include but are not limited to Miglyol® oils, alcohol, IPM, and the like. Mixtures of two or more ar lso usable. Preferably the solvent is Miglyol® 840. The solvent component will comprise about 0.1, to about 99.8%, preferably about 50 to about 80% and most preferably from about 50 to about 70% by weight of the total composition.

The term solvent is intended to include that portion of the formulation which provides the flux of the active ingredient. The preferred solvent is

Miglyol® 840 which is a propylene glycol di-ester of caprylic and capric acids from coconut oil.

The following example illustrates one embodiment of the invention. It is not intended to limit the scope of the invention in any way.

The drug-containing gel composition:

Ingredients	Percent (%) w/w
Diphenhydramine Base	20.0
Miglyol® 840	73.0
Wickenol® 535	0.5
Vit. E Alcohol USP	0.05
Aerosil® 200	6.45

Both Silastic® membrane and polyurethane membranes (with polyester or polyether backbone) were evaluated. In addition the effect of the gelling agent Aerosil® 200 on diphenhydramine flux was determined.

Pharmaceutical compositions containing Miglyol® neutral oils are useful in effecting transdermal delivery of a therapeutic dose of an active drug to the system of mammals. Tables 1-5 below show a series of comparative in vitro diffusion studies illustrating the usefulness of Miglyol® oils, e.g., Miglyol® 840 (Dynamit Nobel Chemicals) as effectively enhancing the penetration of different drugs across biological membranes. Hairless mouse skin was used.

Miglyol® neutral oils, e.g., Miglyol® 812, 810, 818, and 840) are esters of medium chain fatty acids also called fractionated cocoanut oil. Miglyol® 840 is a propylene glycol di-ester of caprylic and capric acids. Miglyol® neutral oils are completely stable against oxidation, tasteless and odorless, soluble in alcohol, nonirritating to the skin.

TABLE I

Comparison of Miglyol® 840's Effect on the Permeation of Tazifylline with Other Skin Permeation Enhancers Across Hairless Mouse Skin

Formulation	Donor Conc.* (mg/ml)	Flux† ($\mu g/cm^2/h$)	Lag Time (h)	Permeability‡ $(cm/sec) \times 10^7$
LA:PG 10:90	6.54	20.48	1.2	8.70
LA:Miglyol® 840 10:90	14.37	33.68	8.47	6.51
DMSO:H_2O 80:20	5.96	25.08	15.97	11.69
ETOH:Miglyol® 840 20:80	52.13	290.58	0.77	15.48
LA:PG:TA 20:30:50	46.07	104.66	8.01	6.31
Miglyol®-Gel: Miglyol® 840:ETOH 66.6:26.7:6.7	15.08	37.33	3.23	6.88
DPH:PG 50:50	16.3	7.81	10.45	1.33

* saturated solution

† Average flux value

‡ Estimated by dividing flux value by initial drug concentration

LA = Linoleic Acid
PG = Propylene Glycol
DMSO = Dimethyl Sulfoxide
TA = Triacetin
ETOH = Ethanol
DPH = Diphenhydramine

TABLE II

Effect of Miglyol® 840 on Diphenhydramine (DPH) Flux Value Across Hairless Mouse Skin

Formulation w/w	Flux† ($\mu g/cm^2/h$)	Lag Time (h)
60:40 Miglyol® 840:DPH	132 ± 21	0
70:30 Miglyol® 840:DPH	118 ± 9	0
90:10 Miglyol® 840:DPH	103 ± 18	0.2 ± 0.2
95:5 Miglyol® 840:DPH	70 ± 19	0.3 ± 0.2
Neat DPH	94	0

† Average flux value

TABLE III

Effect of Miglyol® 840 on Enhancing the Penetration of PD 123,124 Across Hairless Mouse Skin

Solvent System	Drug Conc. (mg/ml)	Flux Value† ($\mu g/cm^2/h$)	Lag Time (h)
Acetone	5	6.46 ± 2.43	1.68 ± 0.67
LA:PG:TA 20:30:50 w/w	20	7.1 ± 5.8	2.65 ± 0.16
Miglyol® 840:ETOH 80:20 w/w	10	41.33 ± 7.68	2.2 ± 0.1

† Average flux value

TABLE IV

Skin Penetration Enhancement Effect of Miglyol® 840 on THA as Compared with Other Penetration Enhancers

Solvent System	Percent (w/w)	Flux Value† ($\mu g/cm^2/h$)	Lag Time (h)
LA:PG:TA 20:30:50 w/w	2	168.6 ± 1.9	2.9 ± 1.3
LA:ETOH:H_2O 5:70:25 w/w	4	645.6 ± 87	6.5 ± 0.5
DPH:PG 50:50 w/w	4	102.45 ± 5.5	5.1 ± 0.56
Miglyol® 840:ETOH 80:20	4	2011.5 ± 117	1.3 ± 0.2
PG	4	106.44	16.6

† Average flux value

TABLE V

Effect of Miglyol® 840 on Penetration of Atenolol Across Hairless Mouse Skin

Solvent System	Percent (w/w)	Flux Value† ($\mu g/cm^2/h$)	Lag Time (h)
PG	4	38.39	22.4
DPH:PG 50:50 w/w	4	148.7 ± 8.76	9.1 ± 2.2
Miglyol® 840:ETOH 80:20 w/w	1	358.01 ± 29	0.5 ± 0.16

† Average flux value

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A transmembranally administerable composition comprising:
(a) about 0.2% to about 5% of therapeutically active medicament of bioaffecting agent,
(b) about 0% to about 99.8% of solvent, and
(c) about 0% to about 15% of gelling agent.

2. A composition of Claim 1 wherein the therapeutically active medicament bioaffecting agent is selected from the group consisting of diphenhydramine, tetrahydroaminoacridine, atenolol, tazifylline, 2-Methoxy-4-[2-(5-methyl-1H-pyrazol-3-yl)ethenyl] phenol or a pharmaceutically acceptable salt thereof.

3. A composition of Claim 1 wherein the solvent is Miglyol® 840.

4. A method of administering a bioaffecting agent comprising contacting a composition of Claim 1 with a living membrane.

5. A transmembranally administerable composition substantially as herein described and exemplified.

DATED this 23rd Day of February, 1989
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